

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Subuphine 0.4 mg sublingual tablets

Subuphine 2 mg sublingual tablets

Subuphine 8 mg sublingual tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

0.4 mg sublingual tablets:

Each sublingual tablet contains buprenorphine hydrochloride corresponding to 0.4 mg buprenorphine.

Excipient with known effect: Lactose 19 mg.

2 mg sublingual tablets:

Each sublingual tablet contains buprenorphine hydrochloride corresponding to 2 mg buprenorphine.

Excipient with known effect: Lactose 48 mg.

8 mg sublingual tablets:

Each sublingual tablet contains buprenorphine hydrochloride corresponding to 8 mg buprenorphine.

Excipient with known effect: Lactose 191 mg.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Sublingual Tablets

Appearance:

0.4 mg tablets: Round, biconvex, white tablets.

2 mg tablets: Oval, biconvex, white tablets with “2” embossed on one side.

8 mg tablets: Oval, biconvex, white tablets with “8” embossed on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment.

4.2 Posology and method of administration

Treatment must be under the supervision of a physician experienced in the management of opiate dependence/addiction.

Treatment with [Buprenorphine] sublingual tablets is intended for use in adults who have agreed to be treated for addiction to opioids.

When treatment with [Buprenorphine] is initiated, the physician should be aware of the partial agonist profile of the buprenorphine molecule. Buprenorphine binds to μ (mu) and κ (kappa) opioid receptors and may trigger withdrawal symptoms in opioid-dependent patients.

Posology

Adults:

Baseline liver function tests and documentation of viral hepatitis status is recommended prior to commencing therapy. Patients who are positive for viral hepatitis, on concomitant medication (see section 4.5) and/or have existing liver dysfunction are at risk of accelerated liver injury. Regular monitoring of liver function is recommended (see section 4.4).

Induction:

Prior to treatment induction, consideration should be given to the type of opioid dependence (i.e. long- or short-acting opioid), the time since last opioid use and the degree of opioid dependence. To avoid precipitating withdrawal, induction with buprenorphine should be undertaken when objective and clear signs of withdrawal are evident.

Initiation therapy

The recommended starting dose is from 0.8 to 4 mg of buprenorphine administered as a single daily dose.

For opioid-dependent drug addicts who have not undergone withdrawal:

When treatment starts, the first dose of [Buprenorphine]sublingual tablet(s) should be administered sublingually at least 6 hours after the last dose of opioid, or when the first signs of withdrawal appear.

For patients receiving methadone:

Before starting treatment with [Buprenorphine], the dose of methadone should be reduced to a maximum of 30 mg/day. The first dose of buprenorphine should be taken when signs of withdrawal appear, but not less than 24 hours after the patient last used methadone. [Buprenorphine] may trigger symptoms of withdrawal in patients treated with methadone.

Dosage adjustment and maintenance:

The dose of [Buprenorphine] should be increased progressively according to the clinical effect of the individual. The mean maintenance daily dose is 8 mg. The majority of patients will not require doses exceeding 16 mg/day, however, the efficacy and safety of buprenorphine tablets was tested in clinical trials in doses up to 24 mg per day.

The dosage is titrated according to reassessment of the clinical status and global management of the patient.

Unsatisfactory stabilisation on 16 mg per day may be related to potential misuse or psychiatric comorbidities. In these cases alternative treatment options should be taken into account.

Especially during initiation of treatment, daily dispensing of buprenorphine is recommended. After stabilisation has been achieved, patients considered trustworthy may

be given a supply of the drug sufficient for several days of treatment. Furthermore local requirements should be followed with regard to dispensing.

Dosage reduction and termination of treatment

After a satisfactory period of stabilisation has been achieved, if the patient agrees, the dosage may be reduced gradually to a lower maintenance dose. When deemed appropriate, treatment may be discontinued. The availability of sublingual tablets in doses of 0.4 mg, 2 mg and 8 mg, allows for a downward titration of the dosage. Patients should be monitored following termination of buprenorphine treatment because of the potential for relapse.

Elderly

No data is available on elderly patients.

Paediatric population

Subuphine is not recommended for use in children and adolescents under the age of 15 years, due to insufficient data on safety and efficacy.

For further information, see the national guidelines for buprenorphine treatment.

Patients with impaired hepatic function

The effect of hepatic impairment on the pharmacokinetics of buprenorphine is unknown. Since the active substance is extensively metabolised, the plasma levels will be expected to be higher in patients with moderate and severe hepatic impairment. As buprenorphine pharmacokinetics may be altered in patients with hepatic insufficiency, lower initial doses and careful dose titration in patients with mild to moderate hepatic impairment are recommended (see section 5.2)

Patients with impaired renal function

Modification of the buprenorphine dose is not required in patients with renal insufficiency. Caution is recommended when dosing patients with severe renal impairment (CL_{cr} < 30 ml/min) (see section 5.2).

Method of administration

Administration of Subuphine is sublingual. The physician must warn patients that the sublingual route is the only effective and safe route of administration for this medicinal product (see section 4.4). The sublingual tablet is to be placed under the tongue until dissolved, which usually occurs within 5 to 10 minutes.

The tablet should not be swallowed, crushed or chewed.

Treatment goals and discontinuation

Before initiating treatment with [Buprenorphine], a treatment strategy including treatment duration and treatment goals, should be agreed together with the patient. During treatment, there should be frequent contact between the physician and the patient to evaluate the need for continued treatment, consider discontinuation and to adjust dosages if needed. When a patient no longer requires therapy with [Buprenorphine], it may be advisable to taper the dose gradually to prevent symptoms of withdrawal (see section 4.4).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1

Severe respiratory insufficiency

Severe hepatic insufficiency

Acute alcoholism or delirium tremens

4.4 Special warnings and precautions for use

Warnings

Tolerance and opioid use disorder (abuse and dependence)

Tolerance, physical and psychological dependence, and opioid use disorder (OUD) may develop upon repeated administration of opioids such as Buprenorphine. Abuse or intentional misuse of Buprenorphine may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders).

Before initiating treatment with Buprenorphine and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see section 4.2).

Patients will require monitoring for signs of drug-seeking behavior (e.g. too early requests for refills). This includes the review of concomitant opioids and psychoactive drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

[Buprenorphine]sublingual tablets are recommended only for treatment of opioid drug dependence. National requirements should be followed with regard to dispensing. Discontinuation of treatment may cause withdrawal symptoms that may be delayed. Due to the lack of data in adolescents (age 15 - <18), buprenorphine should be used only with caution in this age group.

Patients should be closely monitored during the switching period from methadone to buprenorphine since withdrawal symptoms have been reported.

The physician should consider the risk of abuse and misuse (e.g. iv. administration), particularly at the initiation of treatment.

Diversion:

Diversion refers to the introduction of [Buprenorphine] into the illicit market either by patients or by individuals who obtain the medicinal product through theft from patients or pharmacies. This diversion may lead to new addicts using [Buprenorphine] as the primary drug of abuse with the risk of overdose, spread of blood borne viral infections, respiratory depression and hepatic injury. The physician should consider the risk of diversion of buprenorphine into the illicit market before prescribing buprenorphine.

The risk of overdose or treatment dropout is greater if the patient is under treated with buprenorphine and continues to self-medicate withdrawal symptoms with opioids, alcohol or other sedatives and hypnotics (in particular benzodiazepines).

Buprenorphine is a partial agonist at the μ opiate receptor and chronic administration produces dependence of the opioid type.

Precipitated Withdrawal:

When initiating treatment with buprenorphine the physician must be aware of the partial agonist profile of buprenorphine and that it can precipitate withdrawal in opioid-dependent patients particularly if administered less than 6 hours after the last use of heroin or other short-acting opioids, or if administered less than 24 hours after the last dose of methadone (see section 4.2). Conversely, withdrawal symptoms may also be associated with suboptimal dosing.

Buprenorphine can cause drowsiness, which may be exacerbated by other centrally acting agents such as alcohol, tranquilisers, sedatives and hypnotics (see section 4.5).

Animal studies, as well as clinical experience, have demonstrated that buprenorphine may cause dependence but at a lower level than morphine.

Discontinuation of treatment may result in a withdrawal syndrome that may be delayed.

Buprenorphine can cause orthostatic hypotension.

Buprenorphine is an opioid and may mask pain as a disease symptom. Medicinal products that inhibit the enzyme CYP3A4 may cause increased concentrations of buprenorphine. A reduction of the buprenorphine dose may be necessary. In patients who are already treated with CYP3A4 inhibitors the dose of buprenorphine should be titrated carefully since a reduced dose may be sufficient in these patients (see section 4.5).

Concomitant use of monoamine oxidase inhibitors (MAOI) can increase the efficacy of opioids based on experience with morphine. Due to the lack of data in adolescent age 15 - <18, Subuphine should not be used in this age group.

Respiratory depression:

Some cases of death due to respiratory depression have been reported, particularly in cases when used in combination with benzodiazepines (see section 4.5), or when buprenorphine was not used as prescribed. Cases of death have been reported in connection with concomitant administration of buprenorphine and other medical products that causes central nervous system depression such as alcohol or other opioids.

Hepatitis, hepatic disorders:

Cases of acute hepatic injury have been reported in opioid-dependent addicts both in clinical trials and in post-marketing adverse reports. The spectrum of abnormalities ranges from transient asymptomatic elevations in hepatic transaminases to case reports of cytolytic hepatitis, hepatic failure, hepatic necrosis, hepatorenal syndrome, hepatic encephalopathy and death. In many cases the presence of pre-existing liver enzyme abnormalities, genetic disease, infection with hepatitis B or hepatitis C virus concomitant use of other potentially hepatotoxic medicines, alcohol abuse, anorexia, and on-going injecting drug use may have a causative or contributory role. These supplemental factors should be considered before prescribing [Buprenorphine] and during treatment. If a hepatic event is suspected, further biological and aetiological investigation is required. Depending upon the findings, the medicinal product may be discontinued cautiously in order to prevent withdrawal symptoms and to prevent a return to illicit drug use.

If the treatment is continued, hepatic function should be monitored closely.

Sleep-related breathing disorders:

Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion.

In patients who present with CSA, consider decreasing the total opioid dosage.

Paediatric use

No data is available in children less than 15 years of age; therefore, buprenorphine should not be used in children under the age of 15.

Precautions for use

As with other opioids caution should be exercised to patients with:

- asthma or respiratory insufficiency (cases of respiratory depression, have been reported with buprenorphine, see section 4.3);
- renal insufficiency (30 % of the administered dose is eliminated by the renal route; thus renal elimination may therefore be prolonged if renal function is affected);
- hepatic insufficiency (hepatic metabolism of buprenorphine may be altered, see section 4.3);
- head injuries;
- increased intracranial pressure
- hypotension;
- prostatic hypertrophy;
- urethral stenosis

As inhibitors of CYP3A4 (see section 4.5) may increase the concentration of buprenorphine, it is recommended that patients, already treated with inhibitors of CYP3A4, should have their dosage of [Buprenorphine] adjusted carefully since a reduced dose may be sufficient in these patients.

Subuphine sublingual tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Serotonin syndrome

Concomitant administration of “Product name” and other serotonergic agents, such as MAO inhibitors, selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs) or tricyclic antidepressants may result in serotonin syndrome, a potentially life-threatening condition (see section 4.5).

If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

Symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.

If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

The following combinations are not recommended:

Alcohol:

[Buprenorphine] should not be taken together with alcoholic drinks or medicines containing alcohol. Alcohol increases the sedative effect of buprenorphine which will impair the ability to drive or use machinery (see section 4.7).

[Buprenorphine] should be used with caution in combination with:

Benzodiazepines:

This combination may cause death due to respiratory depression of central origin. Therefore dosages must be individually titrated and the patient should be monitored closely. The possibility of drug abuse should also be considered (see section 4.4).

Other central nervous system depressants:

Other opioid derivatives (analgesics and antitussives such as morphine, methadone, dextropropoxyphene, codeine, dextromethorphan and noscapine), certain antidepressants, sedative H1-receptor antagonists, barbiturates, anxiolytics other than benzodiazepines, neuroleptics, clonidine and related substances: This combination increases central nervous system depression and therefore causes a reduced ability to drive and use machinery.

The concomitant use of [Buprenorphine] with gabapentinoids (gabapentin and pregabalin) may result in respiratory depression, hypotension, profound sedation, coma or death (see section 4.4).

Monoamine oxidase inhibitors (MAOI):

Possible exaggeration of the effects of opioids based on experience with morphine.

To date, no notable interaction has been observed with cocaine.

Pharmacokinetic interactions

The effect of other medicinal products on buprenorphine

CYP3A4 inhibitors:

Buprenorphine is metabolised by CYP3A4. An interaction study of buprenorphine with ketoconazole (a potent inhibitor of CYP3A4) resulted in increased C_{max} and AUC (area under the curve) of buprenorphine (approximately 70 % and 50 % respectively) and to a lesser extent, of norbuprenorphine.

Concomitant administration of buprenorphine and [Buprenorphine] potent CYP3A4 inhibitors (such as HIV protease inhibitors like ritonavir, nelfinavir, saquinavir and indinavir or azole antifungal agents such as ketoconazole or itraconazole, erythromycin, gestodene, troleandomycin) can lead to markedly increased plasma concentrations of buprenorphine or norbuprenorphine. The combination should be avoided or monitored closely since a dose reduction may be required.

CYP3A4 inducers:

The interaction between buprenorphine and CYP3A4 inducers has not been investigated. Therefore it is recommended that patients receiving [Buprenorphine] should be closely monitored if enzyme inducers such as phenobarbital, carbamazepine, phenytoin, rifampicin are co-administered.

Effect of buprenorphine on other medicinal products

Buprenorphine has been shown to be a CYP2D6 and CYP3A4 inhibitor in vitro. The risk of inhibition with therapeutic concentrations in vivo seems low, but can not be excluded. When buprenorphine (predominantly at high doses) is combined with medicinal products that are CYP2D6 or CYP3A4 substrates the plasma concentrations of these medicinal products may be increased and the risk of dose dependent adverse reactions may occur. Buprenorphine does not inhibit the enzyme CYP2C19 in vitro. The effect on other enzymes that metabolises medicinal products has not been investigated.

Buprenorphine should be used cautiously when co-administered with:

- Serotonergic medicinal products, such as MAO inhibitors, selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs) or tricyclic antidepressants as the risk of serotonin syndrome, a potentially life-threatening condition, is increased (see section 4.4).

Concomitant administration of buprenorphine with anticholinergics or medications with anticholinergic activity (e.g. tricyclic antidepressants, antihistamines, antipsychotics, muscle relaxants, anti-Parkinson drugs) may result in increased anticholinergic adverse effects.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of [Buprenorphine] in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

During the last three months of pregnancy, continuous use of buprenorphine, regardless of the dosage, may be responsible for a withdrawal syndrome in neonates. Buprenorphine should not be used during second and third trimester of pregnancy. At the end of pregnancy, if high doses have to be given occasionally or if continuous use is necessary, neonatal monitoring should be considered, to prevent a risk of respiratory depression or a withdrawal symptom in children.

Breast-feeding

Buprenorphine and its metabolites are excreted in human breast milk. In rats buprenorphine is excreted in mother's milk and has been found to inhibit lactation. Therefore, breast-feeding should be discontinued during treatment with buprenorphine.

4.7 Effects on ability to drive and use machines

In general buprenorphine has minor to moderate influence on the ability to move safely in traffic, use machines, or perform other hazardous activities. Before stabilization is achieved and opioid tolerance is fully developed, [Buprenorphine] may have major influence on the ability to drive and use machines. [Buprenorphine] can cause drowsiness, dizziness, or impaired thinking, particularly when taken together with other centrally acting substances, including alcohol. Therefore caution is advised if motor vehicles or machines are used (see section 4.4 and 4.5).

4.8 Undesirable effects

The occurrence of undesirable effects depends on the patient's tolerance threshold, which is higher in drug adapted patients than in the general population.

The following frequency convention is used in the evaluation of undesirable effects: Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $\leq 1/100$); rare ($\geq 1/10,000$ to $\leq 1/1,000$); very rare ($\leq 1/10,000$), not known (cannot be estimated from the available data).

Immune system disorders

Very rare: Anaphylactic shock, angioneurotic oedema (Quincke-oedema), bronchospasm

Psychiatric disorders

Common: Anxiety, Nervousness

Uncommon: Hallucinations

Nervous system disorders

Very common: Insomnia

Common: Dizziness, drowsiness, headaches, cases of fainting vertigo

Eye disorders

Common: Lacrimination disorder

Cardiac disorders

Common: ECG abnormalities (QT prolongation)

Vascular disorders

Common: orthostatic hypotension, syncope

Respiratory, thoracic and mediastinal disorders

Common: Rhinorrhoea

Uncommon: Respiratory depression*

Gastrointestinal disorders

Common: Constipation, nausea, vomiting, diarrhoea, abdominal pain

Not known: Dental caries

Hepatobiliary disorders

Uncommon: hepatitis**, hepatic necrosis

Skin and subcutaneous tissue disorders

Common: Sweating

Renal and urinary disorders

Rare: Urine retention

General disorders

Very common: Asthenia, withdrawal syndrome

Common: Back pain, chills

* see section 4.4 and 4.5.

** see section 4.4.

Drug dependence*

Repeated use of Buprenorphine can lead to drug dependence, even at therapeutic doses. The risk of drug dependence may vary depending on a patient's individual risk factors, dosage, and duration of opioid treatment (see section 4.4)

In patients with marked drug dependence, initial administration of buprenorphine may initially produce an antagonist effect similar to that associated with naloxone.

In cases of intravenous misuse local reactions, sometimes septic, and potentially serious acute hepatitis have been reported (see section 4.4).

There have been cases with spontaneous abortion has been reported with buprenorphine. It is not possible to establish a causal relationship, since cases typically involve other drug use or risk factors for spontaneous abortion (see section 4.6).

A neonatal abstinence syndrome has been reported among newborns of women who have received buprenorphine during pregnancy. The syndrome may be milder and more protracted than that from short acting full μ -opioid agonists. The nature of the syndrome may vary depending upon the mother's drug use history (see section 4.6).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions **the national reporting system listed in Appendix V.**

4.9 Overdose

Buprenorphine seems to have a wide therapeutic margin of safety due to its partial opioid agonist properties.

In cases of accidental overdose, general supportive measures should be instituted, including close monitoring of the respiratory and cardiac status of the patient must be monitored closely and relevant symptomatic treatment should be initiated. The major symptom, requiring intervention is respiratory depression, which could lead to respiratory arrest and death.

If the patient vomits, care must be taken to prevent aspiration of the vomit.

Treatment:

Symptomatic treatment of respiratory depression and standard procedures for intensive care should be implemented.

Patent airways and if necessary assisted or controlled ventilation must be assured. The patient should be transferred to an environment within which full resuscitation facilities are available.

Use of an opioid antagonist (e.g. naloxone) is recommended, despite the modest effect it may have in reversing the respiratory symptoms of buprenorphine compared with its effects on full agonist opioid agents, as buprenorphine is strongly attached to the receptor of morphine.

The recommended dose range of naloxone in these cases is 2-8 mg, repeated at suitable intervals.

If an opioid antagonist is used (e.g. naloxone), the long duration of action of buprenorphine should be taken into consideration when determining the length of treatment and medical surveillance needed to reverse the effects of an overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in opioid dependence, ATC code: N07BC01

Mechanism of action:

Buprenorphine is an opioid partial agonist/antagonist which attaches to the μ - and κ -receptors of the brain. Its activity in opioid maintenance treatment is attributed to its slowly reversible binding to the μ -receptors which over a longer period reduces the adapted patients need for drugs.

Opioid agonist ceiling effects were observed during clinical pharmacology studies in opioid dependent persons.

Buprenorphine has a wide therapeutic index due to its partial agonist/antagonist effect, which limits its suppressing effects on especially the cardiac and respiratory function.

5.2 Pharmacokinetic properties

Absorption

When taken orally, buprenorphine undergoes pronounced first-pass hepatic metabolism with N-dealkylation and glucuroconjugation in the small intestine and the liver. The use of this medicinal product by oral route is therefore inappropriate.

Peak plasma concentrations are achieved 90 minutes after sublingual administration and the maximal dose-concentration relationship is linear, between 2 mg and 16 mg.

Distribution

The absorption of buprenorphine is followed by a rapid distribution phase and a half-life of 2 to 5 hours.

Biotransformation

Buprenorphine is metabolised by 14-N-dealkylation and glucuroconjugation of the parent molecule and the dealkylated metabolite. Clinical data confirms that CYP3A4 is responsible for the N-dealkylation of buprenorphine. N-desalkyl-buprenorphine is a μ (mu)- opioid agonist with weak intrinsic activity. Norbuprenorphine contributes to the overall pharmacological effect; however it is unknown to what extent.

Elimination

Elimination of buprenorphine is bi- or tri- exponential, with a long terminal elimination phase of 32 hours. This is in part due to re-absorption of buprenorphine after intestinal hydrolysis of the conjugated derivative, and in part due to the highly lipophilic nature of the molecule.

Buprenorphine is essentially eliminated in the faeces by biliary excretion of the glucuroconjugated metabolites (70 %). The residual 30 % is eliminated in the urine.

Special populations:

Elderly: No pharmacokinetic data in elderly patients available.

Renal impairment: Renal elimination plays a relatively small role (~ 30%) in the overall clearance of buprenorphine. No dose modification based on renal function is required but caution is recommended when dosing subjects with severe renal impairment.

Hepatic impairment: Hepatic elimination plays a relatively large role (~ 70%) in the overall clearance of buprenorphine and the action of buprenorphine may be prolonged in subjects with impaired hepatic clearance. Lower initial buprenorphine doses and cautious titration of dosage may be required in patients with mild to moderate hepatic dysfunction. Buprenorphine is contraindicated in patients with severe hepatic dysfunction (see section 4.3).

5.3 Preclinical safety data

Buprenorphine was not teratogenic in animal studies. Intramuscular doses of 0.05 mg/kg/day and higher caused foetal growth retardation in rats. High doses (1mg/kg/day and higher) resulted in increased perinatal mortality in rats.

A peri-postnatal study with maternal oral administration of buprenorphine at high doses (80 mg/kg/day) during gestation and lactation resulted in difficult parturition (possible as a result of the sedative effect of buprenorphine), high neonatal mortality and a slight delay in the development of some neurological functions (surface righting reflex and startle response) in neonatal rats.

Preclinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity and carcinogenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Mannitol (E421)

Maize starch

Citric acid, anhydrous (E330)

Sodium citrate (E331)

Povidone (E1201)

Magnesium stearate (E470b)

Talc (E553b) (in 0.4 mg sublingual tablets only)

Silica, colloidal anhydrous (in 0.4 mg sublingual tablets only)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This product does not require any special storage conditions.

6.5 Nature and contents of container

0.4 mg sublingual tablets: Blister (PVC/Aluminium).

2 and 8 mg sublingual tablets: Blister (PVC/PVDC/Aluminium).

Pack sizes:

7, 14 and 28 sublingual tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Medicines no longer required should not be disposed of via wastewater or the municipal sewage system. Patients should be instructed to return them to the pharmacy or to ask their pharmacist how to dispose of them in accordance with the national regulations. These measures will help to protect the environment.

7 MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8 MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10 DATE OF REVISION OF THE TEXT

9-Jan-2026